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(54) Title: USE OF MTP INHIBITORS FOR INCREASING LEVELS OF SATIETY HORMONES

(57) Abstract: The present invention relates to the use of inhibitors of microsomal triglyceride transfer protein (MTP) for increasing plasma levels of the satiety hormones such as GLP-1, PYY and CCK.

USE OF MTP INHIBITORS FOR INCREASING LEVELS OF SATIETY HORMONES

[0001] The present invention relates to the use of inhibitors of microsomal triglyceride transfer protein (MTP) for increasing plasma levels of the satiety hormones such as GLP-1, PYY and CCK.

[0002] Microsomal triglyceride transfer protein (hereinafter referred to as MTP) is known to catalyze the transport of triglyceride, cholesteryl ester and phospholipids such as phosphatidylcholine. This indicates that MTP is required for the synthesis of Apo B-containing lipoproteins such as chylomicrons and VLDL, the precursor to LDL. It therefore follows that an MTP inhibitor would inhibit the synthesis of VLDL and chylomicrons, thereby lowering levels of VLDL, LDL, cholesterol and triglyceride in humans. Compounds capable of inhibiting MTP are believed to be useful in the treatment of disorders such as obesity, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, class II diabetes, atherosclerosis and for the reduction of postprandial serum triglyceride plasma levels.

[0003] Satiety hormones are hormones released from the gastrointestinal tract in response to changes in the nutritional state. These hormones influence central mechanisms involved in the regulation of energy balance, through a range of bloodborne and neural pathways.

[0004] Glucagon-like peptide 1 (GLP-1) is an intestinal hormone which generally stimulates insulin secretion during hyperglycemia, suppresses glucagon secretion, stimulates (pro) insulin biosynthesis and decelerates gastric emptying and acid secretion. GLP-1 is secreted from L cells in the small and large bowel following the ingestion of fat and proteins. GLP-1 has been implicated as a possible therapeutic agent for the management of type 2 non-insulin-dependent diabetes mellitus as well as related metabolic disorders, such as obesity.

[0005] Pancreatic polypeptide (“PP”) was discovered as a contaminant of insulin extracts and was named by its organ of origin rather than functional importance. A related peptide was subsequently discovered in extracts of intestine and named Peptide YY (“PYY”) because of the N- and C-terminated tyrosines (Tatemoto, Proc. Natl. Acad. Sci. USA, 79 : 2514 –2518 (1982)). PYY is secreted from the endocrine L cells of the small and large bowel, with high concentration at the terminal ileum, colon and maximum concentration in the rectum. Plasma PYY levels are suppressed in the

fasted state and increase within 30 minutes of nutrients reaching the gut. PYY release is stimulated by nutrient intake in proportion to energy content. It is particularly stimulated by fat intake, compared to carbohydrate and protein meals with a similar calorie content. Recent studies suggest that PYY can induce appetite reduction.

[0006] Cholecystokinin is structurally related to gastrin and exists in several molecular forms with differing numbers of amino acids – examples include CCK-8, CCK-33, CCk-39 and CCK-54. CCK is an endogenous gut hormone found mainly within the duodenum and jejunum and is released following the consumption of food. Release of CCK has been shown to be a satiety signal in humans. When food is consumed, CCK releasing protein (CCKRP) is released in the small intestine. CCKRP stimulates CCK release from the intestinal cells. It has been shown that CCK release results in appetite reduction so that the person will stop eating.

[0007] The ability of CCK to reduce appetite appears to make it a useful agent in the treatment of obesity. An increase in the level of the satiety hormone CCK would result in less food consumed and reduction of hunger cravings between meals. These effects would enable an overweight individual to better comply with a diet that has a reduced caloric intake.

[0008] An increase in the level of the satiety hormone CCK extends the feeling of satiety, resulting in a decrease of food intake which over time results in a decrease in body weight while providing better regulation of glucose and insulin levels following consumption of a meal. The release of CCK also causes a delay in stomach emptying which blunts the post-prandial rise in glucose and insulin. Most persons with Type II diabetes are obese and have an inability to respond normally to insulin. An increase in CCK levels may permit Type II diabetics to be satiated with a lower caloric intake and may offer a better degree of glycemic control.

[0009] Bulimia is an eating disorder characterised by an inability to become satiated by food. As a result bulimics tend to binge on food and regurgitate it to prevent weight gain. Studies have shown that bulimics have a defect in their normal satiety mechanism. Hence an increase of the satiety hormones would permit bulimics to feel satiated.

[0010] Unexpectedly it has now been observed that when inhibitors of microsomal triglyceride transfer protein (MTP) are administered to a mammalian subject, the plasma levels of the satiety hormones such as GLP-1, PYY and CCK are increased.

[0011] The present invention provides the use of a MTP inhibiting compound for the manufacture of a medicament for increasing the levels of satiety hormones, such as the GLP-1, PYY and CCK hormones. Also provided is the use of a pharmaceutical composition comprising a MTP inhibiting compound for the manufacture of a medicament for increasing the levels of satiety hormones, such as the GLP-1, PYY and CCK hormones.

[0012] Further, the present invention provides a method for increasing the levels of satiety hormones, in particular GLP-1, PYY and CCK, in a mammalian subject, which method comprises administering to a mammal a therapeutically effective amount of an MTP inhibiting compound or a pharmaceutical composition comprising a MTP inhibiting compound.

[0013] The use of MTP inhibiting compound for increasing the levels of satiety hormones, in particular the GLP-1, PYY and CCK hormones, also has a lowering effect on the level of glucose in blood plasma and increases insulin sensitivity. Insulin resistance is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty acids in the blood plasma. Insulin resistance in muscle reduces glucose uptake whereas insulin resistance in liver reduces glucose storage, with both effects serving to elevate blood glucose. High plasma levels of insulin and glucose due to insulin resistance often leads to the metabolic syndrome and type 2 diabetes.

[0014] Studies in dogs with an induced dilated cardiomyopathy have shown that a 48 hour of GLP-1 infusion improved the left ventricular function, and reduced systemic vascular resistance compared with saline-treated control animals (Nikolaidis LA et al., Circulation 2004;110:955-961). Accordingly the present invention also relates to the use of MTP inhibiting compounds for increasing the levels of the satiety hormone GLP-1 for the treatment of cardiomyopathy.

[0015] Studies in rats with pyridoxine induced peripheral sensory neuropathy suggest neuroprotection mediated by agonism at the GLP-1 receptor (Perry T. et al, Experimental Neurology 2007:203, 293 – 301). Accordingly the present invention also relates to the use of MTP inhibiting compounds for increasing the levels of the satiety hormone GLP-1 for the treatment of peripheral neuropathies.

[0016] MTP inhibiting compounds have been disclosed in, e.g., Janssen Pharmaceutica : WO-96/13499, WO-02/20501, WO-02/42271, WO-02/081460, WO-2005/058824, and WO-2005/085226; Bristol-Myers-Squibb : EP-0,584,446, EP-0,643,057, WO-96/26205, WO-97/26240, WO-91/43255, WO-97/43257, WO-98/27979, and WO-99/21564; GSK : WO-98/16526, WO-98/47877, WO-98/56790, WO-00/32582, WO-01/92241, WO-01/96327, and WO-03/048121; Japan Tobacco : WO-99/31085, WO-03/072532, and WO-2006/008962; Meji Seika Kaisho : WO-98/54135; Novartis : WO-01/77077 and WO-2000/005201; Pfizer : WO-96/40640, and WO-98/23593.

[0017] Particular MTP inhibiting compounds are, e.g., dirlotapide or (S)-N-{2-[benzyl(methyl)amino]-2-oxo-1-phenylethyl}-1-methyl-5-[4'-(trifluoromethyl)[1,1'-biphenyl]-2-carboxamido]-1H-indole-2-carboxamide; BMS201038 or N-(2,2,2-trifluoroethyl)-9-[4-[4-[[(4'-trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl]amino)-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide (EP-0,643,057); mitratapide or (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (WO-96/13499); (+)-phenyl-(4-{4-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperidin-1-yl)-acetic acid methyl ester (WO-02/20501); JTT-130 or diethyl ester[[[[3-[(dimethylamino)carbonyl]-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]phenyl]acetyl]oxy]methyl]phenyl propanedioic acid (WO-2006/008962); SLx 4090 from Surface Logix; NA-2003 from Meiji Seika Kaisha; [(2R)-2,3-dihydro-5-[[[6-methyl-4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-inden-2-yl]-carbamic acid methyl ester (WO-2000/005201); T-0126 or N-[2-[2-(1H-Pyrazol-1-yl)acetyl]-2,3-dihydro-1H-isoindol-5-yl]-2-[5-(trifluoromethyl)pyridin-2-yl]benzamide from Tanabe Seiyaku (WO-2002/014276).

[0018] As used herein, "mammal" or “mammalian subject” refers to human and non-human patients.

[0019] As used herein, a "therapeutically effective amount" of a MTP inhibiting compound, is the quantity of a compound which, when administered to a mammalian subject, results in a sufficiently high level of that MTP inhibiting compound in the mammalian to cause a discernible increase of the blood plasma levels of the satiety

hormones GLP-1, PYY and CCK.

[0020] The pharmaceutical compositions comprising a MTP inhibiting compound can be administered to a subject either orally, parenterally (for example intravenously, intramuscularly or subcutaneously), percutaneously, or rectally.

[0021] Solid dosage forms for oral administration include capsules, dragees, tablets, powders and granules. These solid dosage forms are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. "Dosage unit form" as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined amount of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

[0022] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, suspo-emulsions, syrups and elixirs. Pharmaceutical compositions for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspension, or emulsions, or may comprise sterile powders for reconstitution into sterile injectable solutions or dispersions.

Description of the drawings

[0023] Figure 1 is a graph displaying plasma CCK (pMol/l) expressed as the median value per group just before the meal and 12 and 24 hours after the meal.

[0024] Figure 2 is a graph displaying the postprandial plasma PYY (pMol/l) levels after 0.02% (w/w) administration of the MTP inhibitor “compound A” mixed in diet containing 17.5% (w/w) (35 kcal%) fat.

[0025] Figure 3 is a graph displaying the postprandial plasma GLP-1 (pg/l) levels after 0.02% (w/w) administration of the MTP inhibitor “compound A” mixed in diet containing 17.5% (w/w) (35 kcal%) fat.

Experimental part

Experiment 1 : Plasma CCK levels – single dose study in dog

[0026] The effect of the MTP inhibitor (+)-phenyl-(4-{4-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperidin-1-yl)-acetic acid methyl ester (WO-02/20501) (hereinafter referred to as "compound A") on CCK plasma levels was studied in 3 groups of 8 dogs each (4 male and 4 female dogs per group). Two groups were treated orally with two different doses of compound A and one group was treated orally with the vehicle and served as a placebo group. The vehicle solution contained the same ingredients as the test formulations with omission of the test substance compound A.

[0027] The treatment groups were :
- group (1) treated orally with vehicle
- group (2) treated orally with 0.15 mg compound A per kg body weight
- group (3) treated orally with 0.63 mg compound A per kg body weight

[0028] Dosing with either vehicle (group 1) or compound A (groups 2 and 3) was done together with a liquid meal at 7.00 hour for the first two males and females of each group and at 18.30 h for the last two males and females of each group. CCK plasma levels were determined before dosing, 0 hour, and at 12 and 24 hours post feeding.

[0029] As seen in Figure 1, plasma CCK (pMol/l) expressed as the median value per group just before the meal and 12 and 24 hours after the meal showed a dose related increase of plasma CCK levels after administration of the MTP inhibiting compound A.

Experiment 2 : Plasma PYY levels – study in rats

[0030] Male Sprauge-Dawley rats (Iffa-Credo) are housed in individually ventilated cages under controlled temperature (20-24°C), humidity (45-65%) and light (12-12h light/dark cycle; Lights on - 5 AM – 5PM). Rats were adapted to a semipurified casein, cornstarch and sucrose based diet (AIN-93) containing 17.5% w/w corn oil as the fat source for 10 days. The 17.5% diet is calculated to contain 35% of energy as fat.

[0031] At dark onset on day 11, half the rats were switched to the same diet containing 0.02% w/w of "compound A", while the remaining rats received the control/adaptation diet. At 0, 1, 2, 4, 6, 12, 14, 16, 20 and 24 hr after diet presentation,

a group of 6 rats/treatment were killed by decapitation and 4 ml of trunk blood was collected in pre-cooled (4°C) K3E plasma tubes containing protease inhibitor cocktail. Blood was centrifuged (1500 x g for 15 minutes at 4°C) within 10-15 minutes of sample collection taking blood sample and stored at -70°C until assayed.

Experiment 3 : Plasma GLP-1 levels – study in rats

[0032] Male Sprauge-Dawley rats (Iffa-Credo) are housed in individually ventilated cages under controlled temperature (20-24°C), humidity (45-65%) and light (12-12h light/dark cycle; Lights on - 5 AM – 5PM). Rats were adapted to a semipurified casein, cornstarch and sucrose based diet (AIN-93) containing 17.5% w/w corn oil as the fat source for 10 days. The 17.5% diet is calculated to contain 35% of energy as fat.

[0033] At dark onset on day 11, half the rats were switched to the same diet containing 0.02% w/w of "compound A", while the remaining rats received the control/adaptation diet. At 0, 1, 2, 4, 6, 12, 14, 16, 20 and 24 hr after diet presentation, a group of 6 rats/treatment were killed by decapitation and 4 ml of trunk blood was collected in pre-cooled (4°C) K3E plasma tubes containing protease inhibitor cocktail. Blood was centrifuged (1500 x g for 15 minutes at 4°C) within 10-15 minutes of sample collection taking blood sample and stored at -70°C until assayed.

Claims

1. Use of a MTP inhibiting compound for the manufacture of a medicament for the treatment of a disease mediated by increasing the levels of satiety hormones.

2. Use according to claim 1 wherein the satiety hormones are GLP-1, PYY and CCK.

3. Use according to claim 2 wherein the satiety hormone is GLP-1.

4. Use according to claim 2 wherein the satiety hormone is PYY.

5. Use according to claim 2 wherein the satiety hormone is CCK.

6. Use of a MTP inhibiting compound for the manufacture of a medicament for increasing the levels of the satiety hormones GLP-1, PYY and CCK and concomitant lowering of glucose levels.

7. Use of a MTP inhibiting compound for the manufacture of a medicament for increasing the levels of the satiety hormones GLP-1, PYY and CCK and concomitant lowering of insulin sensitivity.

8. The use as claimed in claim 2 wherein the disease is cardiomyopathy.

9. The use as claimed in claim 2 wherein the disease is peripheral neuropathies.

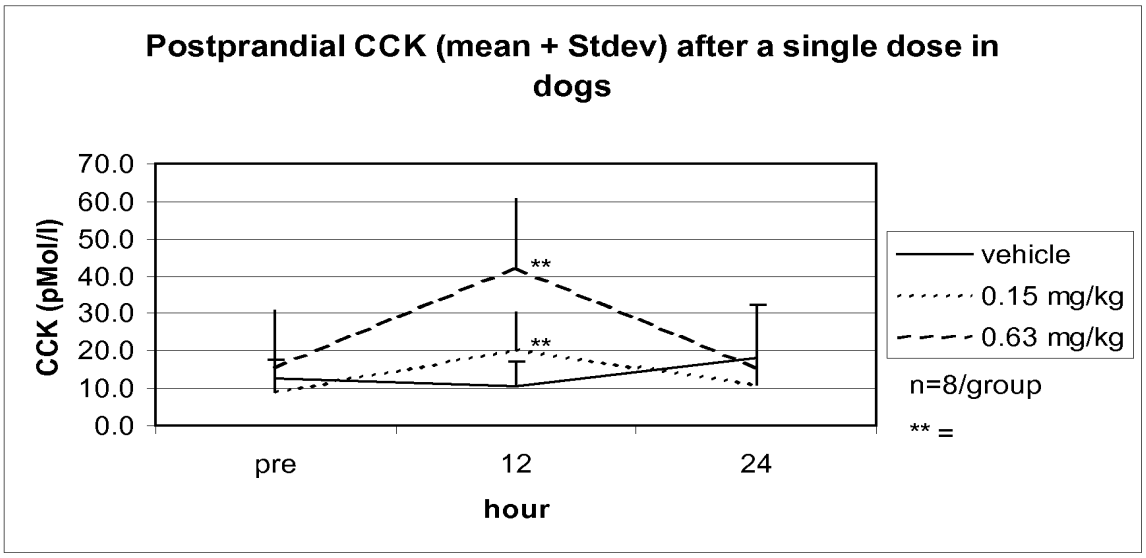
10. The use according to any of claims 1 to 9 wherein the MTP inhibiting compound is selected from dirlotapide , N-(2,2,2-trifluoroethyl)-9-[4-[4-[[(4'-trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl]amino)-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide; (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one; (+)-phenyl-(4-{4-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperidin-1-yl)-acetic acid methyl ester; diethyl ester[[[[3-[(dimethylamino)carbonyl]-4-[[[4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl]carbonyl]amino]phenyl]acetyl]oxy]methyl]phenyl propanedioic acid; [(2R)-2,3-dihydro-5-[[[6-methyl-4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]-carbonyl]amino]-1H-inden-2-yl]-carbamic acid methyl ester (WO-2000/005201); or N-[2-[2-(1H-pyrazol-1-yl)acetyl]-2,3-dihydro-1H-isoindol-5-yl]-2-[5-(trifluoromethyl)pyridin-2-yl]benzamide.

11. The use according to claim 10 wherein the MTP inhibiting compound is (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-

yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one.

12. The use according to claim 10 wherein the MTP inhibiting compound is (+)-phenyl-(4-{4-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperidin-1-yl)-acetic acid methyl ester.

Figure 1 : Plasma CCK (pMol/l) expressed as the median value per group just before the meal and 12 and 24 hours after the meal. Dosing of the MTP inhibitor "compound A" was done together with the meal which consisted of a liquid meal given orally by gavage.



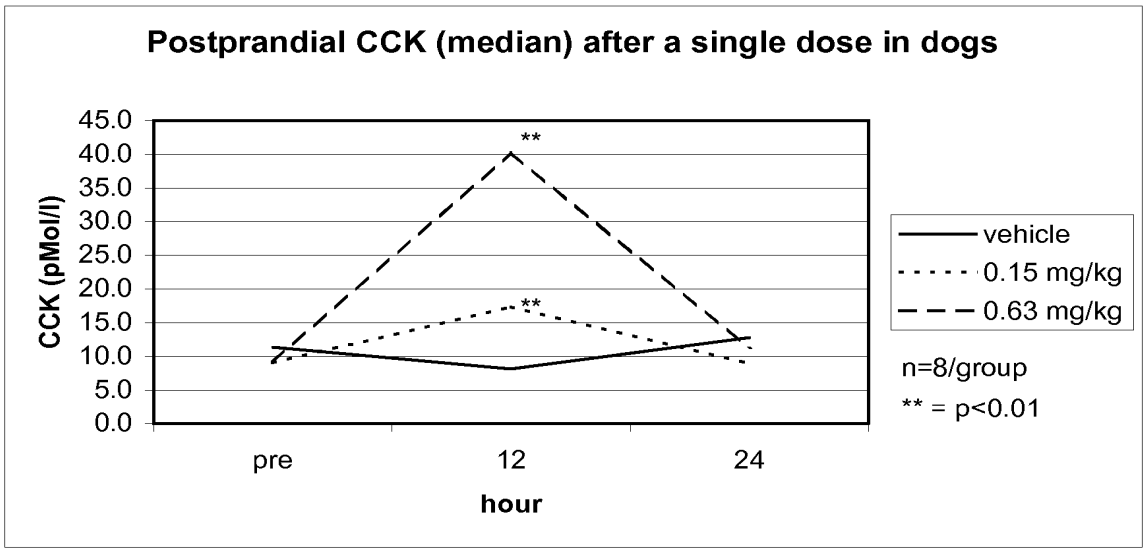


Figure 2 : Postprandial Plasma PYY (pMol/l) levels after 0.02% (w/w) administration of the MTP inhibitor "compound A" mixed in diet containing 17.5% (w/w) fat

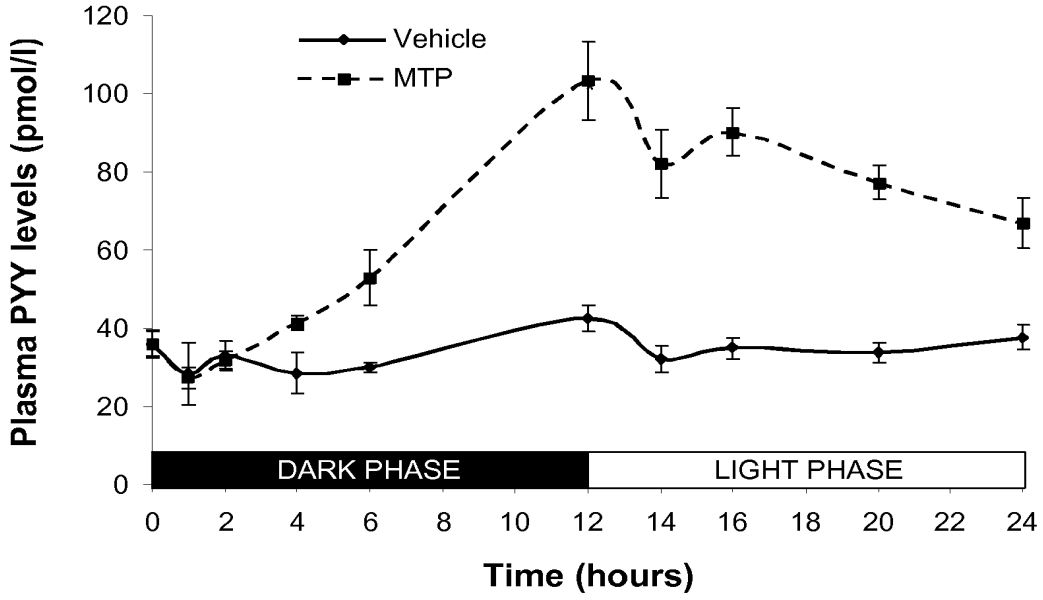
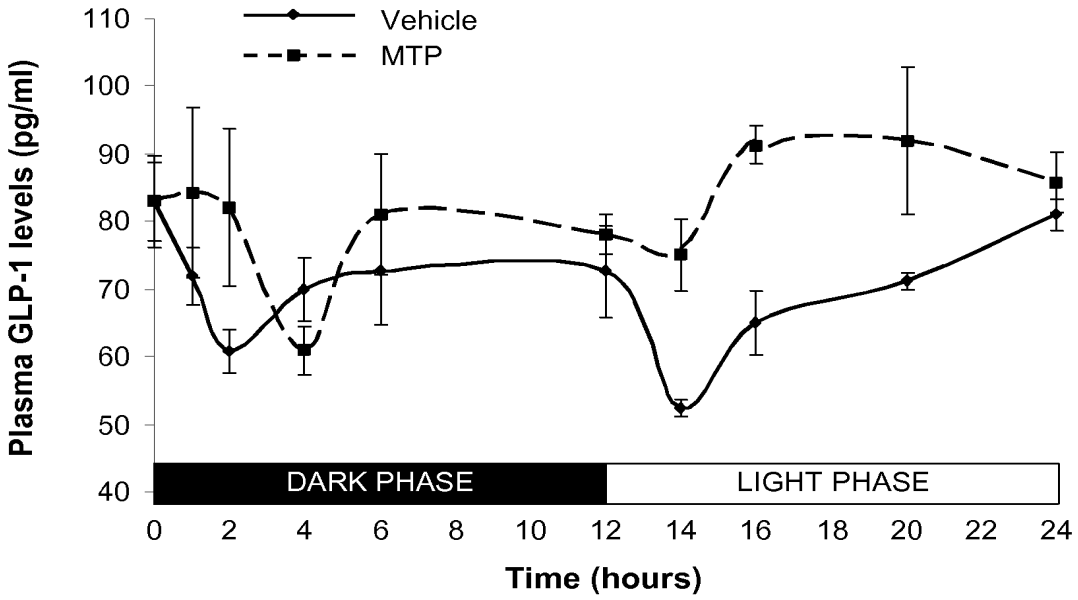


Figure 3 : Postprandial Plasma GLP-1 (pg/l) levels after 0.02% (w/w) administration of the MTP inhibitor "compound A" mixed in diet containing 17.5% (w/w) fat



INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/21 A61K31/216 A61K31/4045 A61K31/4155 A61K31/445
A61K31/4468 A61K31/496 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 099 438 A (PFIZER PROD INC [US]) 16 May 2001 (2001-05-16) abstract page 1, paragraph 4 - paragraph 6 page 3, paragraph 10 page 12, paragraph 105 -----	1-7,10
X	WO 2005/046644 A (PFIZER PROD INC [US]; FRIESEN DWAYNE THOMAS [US]; SHANKER RAVI MYSORE) 26 May 2005 (2005-05-26) page 1, line 5 - line 8 page 2, line 15 - line 21 page 4, line 17 ----- -/--	1-7,10

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Damiani, Federica

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 712 279 A (BILLER SCOTT A [US] ET AL) 27 January 1998 (1998-01-27) column 1, line 15 - line 18 column 23 column 40, line 25 - line 34	1-7,10
X	WO 00/05201 A (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; FINK CYNTHIA ANNE) 3 February 2000 (2000-02-03) cited in the application page 20, paragraph 3 page 84; example 14	1-8,10
X	JP 2003 231635 A (TANABE SEIYAKU CO) 19 August 2003 (2003-08-19) abstract	1-7,10
X	WO 2006/008962 A (JAPAN TOBACCO INC [JP]; FURUKAWA NOBORU [JP]; MERA YASUKO [JP]; KAWAI) 26 January 2006 (2006-01-26) cited in the application abstract	1-7,10
X	WO 2005/070390 A (JANSSEN PHARMACEUTICA NV [BE]; FRANCOIS MARC KAREL JOZEF [BE]; EMBRECH) 4 August 2005 (2005-08-04) page 1, paragraphs 1,2 page 7, paragraph 25	1-8,10, 11
X	WO 02/20501 A (JANSSEN PHARMACEUTICA NV [BE]; MEERPOEL LIEVEN [BE]; ROEVENS PETER WAL) 14 March 2002 (2002-03-14) cited in the application example B.10; tables F-1 page 25, line 1 - line 8 page 25, line 24 - line 30	1-7,10, 12
X	WO 00/53171 A (MOLTENI L E C DEI FRATELLI ALI [IT]; MANNUCCI EDOARDO [IT]; ROTELLA CA) 14 September 2000 (2000-09-14) page 1, line 5 - line 8 page 8	1-7
X	WO 2004/022074 A1 (NOVARTIS NUTRITION AG [CH]; HUGHES THOMAS EDWARD [US]; WESTERTERP-PLAN) 18 March 2004 (2004-03-18) abstract page 1, line 1 - line 4 page 3, line 5 - line 9 page 2, line 26	1-7,9

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INTERNATIONAL SEARCH REPORT

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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